Application Serial No.: 10/801,608
Inventor(s): Allegrini *et al.*
Attorney Docket No.: 100506-00023

I. AMENDMENTS TO THE SPECIFICATION

Page 2, lines 5 to 15:

A known medicament that contains a sulfinyl group is ~~modafinil~~ Modafinil, i.e. 2-[(diphenylmethyl)sulfinyl]acetamide. According to various synthetic methods, intermediate 2-[(diphenylmethyl)thio]acetic acid or 2-[(diphenylmethyl)thio]acetamide is oxidized with hydrogen peroxide to give 2-[(diphenylmethyl)sulfinyl]acetic acid, or 2-[(diphenylmethyl)sulfinyl]acetamide, respectively. This oxidation, usually performed with 110 volumes hydrogen peroxide, involves safety problems. Similar problems also occur in the synthesis of other biologically active sulfinyl compounds, such as ~~sulindac~~ Sulindac, i.e. (Z)-5-fluoro-2-methyl-1-[[4-(methyl-sulfinyl)phenyl]methylene]-1H-indene-3-acetic acid, and the so-called "prazoles", i.e. [[(pyridyl)methyl]sulfinyl]benzimidazole derivatives, which are known anti-secretory agents.

Page 3, lines 10 to 25:

The process of the invention is particularly useful for the preparation of biologically active compounds containing sulfinyl or sulfonyl groups, such as ~~modafinil~~ Modafinil; ~~modafinil-sulfone~~ Modafinil-sulfone (i.e. ~~modafinil-sulfone~~ Modafinil-sulfone analogue); ~~sulindac~~ Sulindac; ~~sulindac-sulfone~~ Sulindac-sulfone (i.e. ~~sulindac-sulfone~~ Sulindac-sulfone analogue); ~~dapsone~~ Dapsone; and [[(pyridyl)methyl]sulfinyl]benzimidazole derivatives, known as anti-secretory agents, such as those disclosed in WO 01/04109 and EP 998944, in particular:

~~omeprazole~~ Omeprazole, i.e. 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole;

~~pantoprazole~~ Pantoprazole, i.e. 5-difluoromethoxy-2[[3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole;

~~lansoprazole~~ Lansoprazole, i.e. 2-[[[methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

~~timoprazole~~ Timoprazole, i.e. 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole);

~~picoprazole~~ Picoprazole, i.e. 5-ethoxycarbonyl-6-methyl-2[[(3-methyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole;

~~rabeprazole~~ Rabeprazole, i.e. 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;

~~exomeprazole~~ Exomeprazole, i.e. the (S)-isomer of ~~omeprazole~~ Omeprazole.

Page 4, lines 1 to 9:

- intermediates for the preparation of ~~sulindac~~ Sulindac, in particular those disclosed in U.S. Pat. No. 3,647,858, such as 1-(4-fluorophenyl)-2-(4-methylthio-phenyl)-ethanone and (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid; preferably (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid;
- intermediates for the preparation of ~~modafinil~~ Modafinil, such as 2-[(diphenylmethyl)thio]acetic acid and 2-[(diphenylmethyl)thio]acetamide;
- intermediates for the preparation of ~~dapsone~~ Dapsone, such as 4,4'-thiobisbenzenamine;

Page 5, lines 4 to 7:

Examples of intermediate compounds containing a sulfinyl group are ~~sulindac~~ Sulindac, ~~modafinil~~ Modafinil, 1-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-ethanone, and 2-[(diphenylmethyl)sulfinyl]acetic acid.

Page 7, lines 10 to 12:

Preparation of (5-difluoromethoxy)-2-[(4-chloro-3-methoxy-2-pyridinyl)methylsulfinyl-1H-benzimidazole (Intermediate for the Preparation of ~~pantoprazole~~ Pantoprazole)

Page 8, line 17 to page 9, line 2:

Using the same procedure, the following compounds can be prepared:

~~omeprazole~~ Omeprazole from 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole;

~~pantoprazole~~ Pantoprazole from 5-difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole;

~~lansoprazole~~ Lansoprazole from 2-[[[methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole;

~~timoprazole~~ Timoprazole from 2-[[(2-pyridinyl)methyl]thio]-1H-benzimidazole;

~~picoprazole~~ Picoprazole from 5-ethoxycarbonyl-6-methyl-2[[(3-methyl-2-pyridinyl)methyl]thio]-1H-benzimidazole;

~~rabeprazole~~ Rabeprazole from 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole; and

~~exomeprazole~~ Exomeprazole from (S)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

Page 9, lines 4 to 5:

Preparation of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (~~sulindac~~ Sulindac)

Page 9, lines 6 to 13:

(Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid (5 g, 14.7 mmoles) is dissolved in dichloromethane (25 ml). The solution is added with 5.4 g (14.26 mmoles) of 73% w/w phthalimidoperhexanoic acid, keeping the temperature at about 20°C. After 18 h, the solution is concentrated to a residue that is crystallized from 15 ml methanol. After drying, 4.8 g of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (~~sulindac~~ Sulindac) is obtained. Molar yield: 91%.

Page 9, line 25 to page 10, line 4:

Preparation of ~~sulindac~~ Sulindac

(Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid (5 g, 14.7 mmoles) is dissolved in methanol (40 ml). The solution is added with 5.4 g (14.26 mmoles) of 73% w/w ε-phthalimidoperhexanoic acid, keeping the temperature at about 20°C. After 18 h, the solution is concentrated to 15 ml and cooled to 5°C. The

precipitate is filtered and dried. 4.6 g of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl) phenyl]methylene]-1H-indene-3-acetic acid (~~sulindac~~ Sulindac) is obtained.

Page 10, lines 13 to 15:

2-[(diphenylmethyl)sulfonyl]acetic acid from 2-[(diphenylmethyl)sulfinyl]acetic acid; and 2-[(diphenylmethyl)sulfonyl]acetamide (~~modafinil sulfone~~ Modafinil-sulfone) from 2-[(diphenylmethyl)sulfinyl]acetamide.

Page 10, lines 17 to 23:

Preparation of ~~modafinil~~ Modafinil

10 g (38.9 mmoles) of 2-[(diphenylmethyl)thio]acetamide are dissolved in 100 ml of dichloromethane. The solution is added with 15.7 g of 68% w/w ε-phthalimidoperhexanoic acid, keeping the temperature at about 20°C, and after 6 h is diluted with water, adjusting the pH to 8-9 with aqueous ammonia. The resulting phases are separated and the organic one is evaporated to dryness, to obtain 8.5 g of 2-[(diphenylmethyl)sulfinyl]acetamide (~~modafinil~~ Modafinil). Molar yield: 80%.

Page 11, lines 4 to 10:

Preparation of ~~modafinil sulfone~~ Modafinil-sulfone

10 g (38.9 mmoles) of 2-[(diphenylmethyl)thio]acetamide are dissolved in 100 ml of dichloromethane. The solution is added with 31.4 g of 68% w/w ε-phthalimidoperhexanoic acid, keeping the temperature at 20°C and after 6 h is diluted with water, adjusting the pH to 8-9 with aqueous ammonia. The resulting phases are separated and the organic one is evaporated, to obtain 8.1 g of 2-[(diphenylmethyl) sulfonyl]acetamide (~~modafinil sulfone~~ Modafinil-sulfone).

Page 11, lines 16 to 23:

Using the same procedure, the following compounds can be prepared: 2-[(diphenylmethyl)sulfonyl]acetic acid from 2-[(diphenylmethyl)thio]acetic acid; 1-(4-fluorophenyl)-2-(4-methylsulfonyl-phenyl)-ethanone from 1-(4-fluorophenyl)-2-(4-methylthiophenyl)-ethanone; (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfonyl)-

phenyl]methylene]-1H-indene-3-acetic acid from (Z)-5-fluoro-2-methyl-1-[[4-(methylthio)-phenyl]methylene]-1H-indene-3-acetic acid; and 4,4'-sulfonylbenzenamine (~~dapsone~~ Dapsone) from 4,4'-thiobisbenzenamine.